

What is claimed is:

1. A method of treating a mammalian organism suffering from a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in cells, comprising the step of administering to said mammalian organism a composition, said composition comprising a compound effective to inhibit the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function.
2. A method according to claim 1 wherein said cells comprise endothelial cells.
3. A method according to claim 2 wherein said organism is human.
4. A method according to claim 3 wherein said compound comprises a polypeptide selected from the group consisting of:
  - (a) a polypeptide comprising an antigen-binding fragment of an anti-Flt4 antibody;
  - (b) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand;
  - (c) a polypeptide comprising a fragment or analog of a vertebrate vascular endothelial growth factor C (VEGF-C) polypeptide, wherein said polypeptide and said fragment or analog bind said Flt4 expressed on native host cells;
  - (d) a polypeptide comprising a fragment or analog of a vertebrate vascular endothelial growth factor-D (VEGF-D) polypeptide, wherein said polypeptide and said fragment or analog bind said Flt4 expressed on native host cells.

5. A method according to claim 4 wherein said compound further comprises a detectable label.

6. A method according to claim 4 wherein said composition further comprises a pharmaceutically acceptable diluent, adjuvant, or carrier medium.

7. A method according to claim 4 wherein said compound comprises an anti-Flt4 antibody or fragment thereof.

8. A method according to claim 3 of treating a mammalian organism suffering from a neoplastic disease characterized by expression of Flt4 tyrosine kinase (Flt4) in vascular endothelial cells, comprising the steps of:  
administering to a mammalian organism in need of such treatment a composition, said composition comprising a compound effective to inhibit the binding of an Flt4 ligand protein to Flt4 expressed in vascular endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of said vascular endothelial cells.

9. A method according to claim 8 wherein said neoplastic disease is selected from the group consisting of carcinomas, squamous cell carcinomas, lymphomas, melanomas, and sarcomas.

10. A method according to claim 8 wherein said neoplastic disease is a breast carcinoma characterized by expression of Flt4 in vascular endothelial cells.

11. A method according to claim 10 wherein said compound comprises a polypeptide comprising an antigen-binding fragment of an anti-Flt4 antibody.

12. A method according to claim 10 wherein said compound comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

5                   13. A method according to claim 12 wherein said blood vascular endothelial marker antigen is selected from the group consisting of PAL-E, VEGFR-1, and VEGFR-2.

10                   14. A method according to claim 12 wherein said compound further comprises an anti-neoplastic agent conjugated to said bispecific antibody.

15                   15. A method for screening a biological sample for the presence of Flt4 receptor tyrosine kinase protein (Flt4), comprising the steps of:

                    (a) contacting a biological sample suspected of containing Flt4 with a composition comprising an Flt4 binding compound, under conditions  
15                   wherein said compound will bind to Flt4 in said biological sample;

                    (b) washing said biological sample under conditions that will remove Flt4 binding compound that is not bound to Flt4 in said sample; and

                    (c) screening said sample for the presence of Flt4 by detecting  
20                   Flt4 binding compound bound to Flt4 receptor tyrosine kinase in said sample after said washing step.

16. A method according to claim 15 wherein said compound comprises a polypeptide selected from the group consisting of:

                    (a) a polypeptide comprising an antigen-binding fragment of an anti-Flt4 antibody; and

25                   (b) a polypeptide comprising an Flt4 ligand or Flt4 binding fragment thereof.

17. A method according to claim 15 wherein said compound comprises antibody that specifically binds Flt4, said antibody further comprising a detectable label.

5 18. A method for imaging vertebrate tissue suspected of containing cells that express Flt4 receptor tyrosine kinase protein (Flt4), comprising the steps of:

(a) contacting vertebrate tissue with a composition comprising an Flt4 binding compound; and

10 (b) imaging said tissue by detecting said Flt4 binding compound bound to said tissue.

19. A method according to claim 18 wherein said Flt4 binding compound is selected from the group consisting of an Flt4 ligand polypeptide, an antibody that specifically binds Flt4, and antibody fragments that specifically bind Flt4.

15 20. A method according to claim 18 wherein said Flt4 binding compound is an antibody that specifically binds Flt4.

21. A method according to claim 20, wherein said antibody further comprises a detectable label covalently bound thereto.

20 22. A method according to claim 21, wherein said tissue comprises human tissue.

23. A method according to claim 20, further comprising the step of washing said tissue, after said contacting step and before said imaging step, under conditions that remove from said tissue antibody that is not bound to Flt4 in said tissue.

24. A method for detecting Flt4 receptor tyrosine kinase (Flt4) expressed on the surface of cells in a vertebrate organism, comprising the steps of:

- 5 (a) administering a composition to a vertebrate organism, said composition comprising an antibody that specifically binds Flt4 or an antigen-binding fragment thereof; and
- (b) detecting antibody or said fragment bound to cells in said organism, thereby detecting Flt4 expressed on the surface of cells in said organism.

10 25. A method according to claim 24, wherein said organism is human and wherein said antibody or antibody fragment further comprise a detectable label.

26. A method of screening for a neoplastic disease state, comprising the steps of:

- 15 (a) contacting tissue from a mammalian organism suspected of having a neoplastic disease state with a composition comprising an antibody or antibody fragment that specifically binds Flt4 receptor tyrosine kinase;
- (b) detecting said antibody or antibody fragment bound to cells in said mammalian organism; and
- 20 (c) screening for a neoplastic disease from the quantity or distribution of said antibody bound to cells in said mammalian organism.

27. A method according to claim 26 wherein in said screening step, the detection of said antibody or antibody fragment bound to blood vessel endothelial cells is correlated with the presence of a neoplastic disease.

25 28. A method according to claim 27 wherein said tissue comprises mammary tissue.

29. A method of screening for a disease characterized by a change in lymphatic vessels or high endothelial venules, comprising the steps of:

- 5 (a) obtaining a tissue sample from a vertebrate organism suspected of being in a diseased state characterized by changes in lymphatic cells or high endothelial venules;
- (b) exposing said tissue sample to an antibody that specifically binds Flt4 receptor tyrosine kinase expressed by cells in said organism;
- (c) washing said tissue sample; and
- 10 (d) screening for said disease by detecting the presence of said antibody in said tissue sample.

30. A method according to claim 29, wherein said disease is selected from the group consisting of metastatic cancer, lymphoma, acute inflammation, chronic inflammation, infection and immunological disease.

15 31. A method for imaging lymphatic vessels or high endothelial venules (HEVs) in a mammalian tissue, comprising the steps of:

- (a) contacting said tissue with an antibody that specifically binds a mammalian Flt4 receptor tyrosine kinase protein; and
- (b) imaging said vessels or HEVs by detecting said antibody
- 20 bound to said tissue.

32. A method according to claim 31 wherein said antibody further comprises a detectable label covalently bound thereto.

33. A method according to claim 32, wherein said tissue comprises human tissue.

34. A method according to claim 32, further comprising the step of washing said tissue sample, after said contacting step and before said imaging step, under conditions that remove from said tissue antibody that is not bound to Flt4 receptor tyrosine kinase protein in said tissue.

5                   35. A method for detecting lymphatic vessels, lymphatic tissue, or high endothelial venules (HEVs) in a mammal, comprising the steps of:

(a) administering to said mammal a composition comprising an antibody that specifically binds a mammalian Flt4 receptor tyrosine kinase, and

10                   (b) detecting said antibody bound to lymphatic vessels, lymphatic tissues, or high endothelial venules in said organism, thereby detecting said lymphatic vessels, lymphatic tissues, or high endothelial venules in said organism.

36. A method according to claim 35, wherein said mammal is human.

15                   37. A method of screening for a disease characterized by a change in lymphatic vessels or high endothelial venules, comprising the steps of:

20                   (a) obtaining a tissue sample from a vertebrate organism suspected of being in a diseased state characterized by changes in lymphatic cells or high endothelial venules;

(b) exposing said tissue sample to an antibody that specifically binds Flt4 receptor tyrosine kinase expressed by cells in said organism;

(c) washing said tissue sample; and

25                   (d) screening for said disease by detecting the presence of said antibody in said tissue sample.

38. The method according to claim 37, wherein said disease is selected from the group consisting of metastatic cancer, lymphoma, acute inflammation, chronic inflammation, infection and immunological disease.

5 39. A method of screening for a disease characterized by a change in neovascular endothelial cells, comprising the steps of:

(a) obtaining a tissue sample from a vertebrate organism suspected of being in a diseased state characterized by changes in neovascular endothelial cells;

10 (b) exposing said tissue sample to a composition comprising a compound that specifically binds Flt4 receptor tyrosine kinase expressed by cells in said organism;

(c) washing said tissue sample; and

(d) screening for said disease by detecting the presence, quantity, or distribution of said compound in said tissue sample.

15 40. A method for detecting neovascular endothelial cells in a mammal, comprising the steps of:

(a) administering to said mammal a composition comprising a first compound that specifically binds a mammalian Flt4 receptor tyrosine kinase, and

20 (b) detecting said first compound bound to neovascular endothelial cells, thereby detecting neovascular endothelial cells in said organism.

41. A method according to claim 40, further comprising administering to said mammal a second compound that specifically binds to a blood vessel endothelial marker; and wherein said detecting step comprises detection of said first and said second compound bound to neovascular endothelial cells.

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42. A method according to claim 4, wherein said disease comprises Kaposi's sarcoma.